Claim 19, line 3.

Cancel claim 21.

REMARKS

The indication by the Examiner that changing PEG in the claims to PEG 200 would overcome the 35 U.S.C. 112 rejection is gratefully acknowledged. By the present amendment, this has been done.

In the final rejection, the Examiner quotes a portion of a statement from the Declaration of Dr. Duffy, namely, that "the increase in viscosity renders PEG 400 completely unsuitable for use in the composition of this invention ...". PEG 400 would be unsuitable as the solvent because of its elongated filter times, the syringeability of the parenteral product and the potential of irritancy to the target animal. However, it is further pointed out that the use of PEG 400 in the PEG ranges specified by the claims in the present application does not exhibit the unsuitable characteristics when it is combined with glycerol formal in the ranges specified in the claims in the present application. Thus, PEG 400 will not act suitably in the present application by itself but will work suitably when used in combination with glycerol formal as called for by the claims.

In regard to the above, it may be useful to reiterate certain points about formulation of oxytetracycline at high levels. Zupan was allowed over Ghilardi (US 4,020,162) which proposed a range of

PEG 300 - 600 , in practice PEG 400, to attain 1 - 12% oxytetracycline, a very low level compared with the objectives of the present invention which achieves up to 35%. Zupan describes up to 25% oxytetracycline, which was achievable by adopting magnesium oxide in place of other apparently equivalent salts such as magnesium chloride. Zupan is silent about the duration of effective activity. The product of the present invention can contain up to 35% w/v oxytetracycline (page 3, lines 33 - 35) and provide for a pharmaco-kinetically long-acting product capable of achieving effective plasma levels against susceptible organisms in excess of 9 days (page 2, lines 3 - 6).

The applicants submit that it cannot be shown that from the readings of the prior art available that the objective was obviously achievable by applying the teachings of say Zupan and Hacke alone or in combination.

The Hacke invention lay in the finding that glycerol formal could be an effective co-solvent in combination with certain magnesium compounds. A person of ordinary skill following Hacke would not be motivated to substitute glycerol formal in whole or in part. To do so would be to disregard the Hacke teachings and embark on uncharted waters, i.e. to risk failure and conduct research away from Hacke's teachings. Hacke can be considered as closest art only from a point of view of its use of glycerol formal as co-solvent in an oxytetracycline formulation.

Alternatively, faced with Zupan, which appears closer in

achieving the desired objective of the present invention in view of Zupan's unsupported mere assertion of up to 30% by weight of oxytetracycline, the ordinary artisan of no inventive capacity would understand that only polyethylene glycol, especially PEG 400 as described, would be expected to be successful, provided that magnesium oxide was used rather than any other magnesium salt stabilizer.

Nothing in Zupan would lead one of ordinary skill to reason that another co-solvent could be substituted in whole or in part for PEG 400. The prosecution history of Zupan plainly shows that Zupan's invention was selection of magnesium oxide particularly for use with PEG 400 as the co-solvent with water. The file wrapper also contains cogent arguments as to the non-equivalence of PEG 400 and glycerol formal. These technical differences are scientific facts that can reasonably be attributed to the person of ordinary skill in the field of chemistry. Thus, based on technical comprehension of the materials under discussion and the teachings of Zupan, there can be no expectation that the person of ordinary skill and knowledge would find it reasonable, never mind obvious, to substitute glycerol formal for polyethylene glycol 400 with any expectation of success. Therefore, as it was considered unreasonable to combine Ghilardi and Hacke against the claims of the Zupan patent, analogously, it is even more unreasonable in the present case where there is not a replacement of one for the other but in fact a mixed co-solvent system.

Faced with a complex molecule like oxytetracycline, which is lipophilic, and the fact that the art reflects extreme difficulty in formulating stable compositions thereof, a prima facie showing of obviousness has not been made out on the art cited. The art indicates a distinct preference for adopting a single co-solvent with particular magnesium salts such as stabilizers. Nothing points to the adoption of more than one co-solvent. Based upon the teachings of Hacke and/or Zupan, there can be no reasonable expectation that one would achieve, for example, a higher percentage of oxytetracycline i.e. up to 35% by adopting a mixed solvent system.

The present invention provides a stable composition containing up to 35% oxytetracycline which remains suitable for use, i.e. has an effective shelf life when stored according to industry practice, for at least 24 months. There is no reason to derive from either Hacke or Zupan an expectation that altering the co-solvent system from that specifically taught therein would lead to success in stability.

In contrast to the available art, the applicants have achieved significantly different results and unpredictable success by adopting a mixed co-solvent system utilizing glycerol formal and polyethylene glycol. PEG 200 is not the only PEG that can be used in the invention.

The present application has sought to protect the mixed co-solvent system adopting 10 - 50% glycerol formal with 1 - 15% PEG.

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The non-obviousness of adopting a mixed co-solvent system has been addressed above.

Applicants are proposing operating outside the limits of PEG specifically taught in the art, i.e. Zupan, and moreover using a solvent system (water:GF;PEG) offering significant commercial advantages especially in terms of long term stability, and long-acting effect (pharmaco-kinetically long-acting product capable of achieving effective plasma levels, against susceptible organisms in excess of 9 days. The prior art could not deliver such a product.

A Notice of Allowance is respectfully requested.

Respectfully submitted,

Date: 3-14-00

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231, on the date of signature identified below.

John P. Shannon, Registration No. 29,276

Signature

Date of Signature 3-14-00